

practicing the invention using donor cells and recipient oocytes of different ungulate species, Bos gaurus and Bos taurus, of the same subfamily (bovine); and also in original claims 6 and 49, which describe using donor cells and recipient oocytes of different ungulate species. New claims 133-140 recite an ungulate animal developed from a nuclear transfer unit produced by the claimed method; support for which is found in Example 2, which describes the successful generation of fetal and developed animals produced by the claimed method of cross-species nuclear transfer. The amendment does not introduce new matter.

Regarding Rejection of the Claims Under 35 U.S.C. §112, First Paragraph:

Claims 51-78, 86-111, and 125-137 were rejected under 35 U.S.C. §112, first paragraph, because the claims broadly encompass methods resulting in production of xenomitochondrial cybrids comprising incompatible nuclei and mitochondria so that the resulting nuclear transfer unit is incapable of developing. The amended claims expressly limit the claimed invention to methods and products wherein the resulting multicellular nuclear transfer unit is able to develop into an ungulate mammal having genomic DNA of one ungulate species and mitochondria of a different ungulate species upon being transferred into a female animal of the same species as the oocyte, as described in the disclosed example. Additional support for the method is provided by Saikhun et al. (2002, Theriogenology, 57(7):1829-37, abstract attached), which describes successful production of an animal by cross-species nuclear transfer, using a nuclear donor cell of bison (*Bubalus bubalis*) and an oocyte of *Bos indicus*. The development of nuclear transfer units produced by the claimed method of cross-species nuclear transfer into fully formed animals demonstrates the totipotency of the cells of the nuclear transfer units produced by the claimed method; so that persons skilled in the art would be able to practice the described method and produce the recited bovine cells and animals successfully without having to perform undue experimentation.

Methods for genetically modifying somatic cells of domestic animals, and then using the genetically altered cells as nuclear donor cells in cloning by nuclear transfer, as described in the application and as recited in claim 86, have become routine practice in the art. For example, see Phelps et al., *Science*, 2003, 299:411-414, a copy of which is attached.

The Applicants submit that the specification enables one skilled in the art to make and use the claimed invention without undue experimentation, and they respectfully request withdrawal of the rejection of the claims as non-enabled under 35 U.S.C. §112, 1st Paragraph.

Regarding Rejection of the Claims Under 35 U.S.C. §112, Second Paragraph:

Claims 51-82, 86-116, and 125-132 were rejected under 35 U.S.C. §112, second paragraph, because the precise meaning of the phrase "removing the genomic DNA from a mammalian oocyte" in step (i) of claims 51 and 86 was considered unclear. Claims 51 and 86 are amended by replacing the phrase "removing the genomic DNA" with "enucleating." Withdrawal of the rejection of the claims under 35 U.S.C. §112, 2nd paragraph, is respectfully requested.

Rejection of Claims Under 35 U.S.C. §102(b) as being anticipated by Heyneker et al.:

Claims 79-85, 112-124, and 128-135 were rejected under 35 U.S.C. §102(b) as being anticipated by Heyneker *et al.* (1991), which discloses transgenic, isolated embryonic cells having non-bovine genomic DNA and bovine mitochondria. The Applicants submit that Heyneker *et al.* do not describe or suggest making the claimed cells derived from an embryo produced by cross-species nuclear transfer and having a genome of one ungulate species, and mitochondria of a different ungulate species. Accordingly, withdrawal of the rejection of the claims under 35 U.S.C. §102(b) as being anticipated by Heyneker *et al.* is respectfully requested.

Rejection of Claims Under 35 U.S.C. §102(b) as being anticipated by Capecchi (1994):

Claims 79, 81, 83, 84, 112, 114, 117, 118, 121, 123, 128, and 130 were also rejected under 35 U.S.C. §102(b) as being anticipated by Capecchi (1999), which discloses mice genetically modified by homologous recombination to have human DNA inserted in their genomes. The Applicants submit that the cells disclosed by Capecchi do not have a genome of one ungulate species and mitochondria of a different ungulate species as recited in the present claims. Accordingly, Applicants respectfully request that the rejection of claims under 35 U.S.C. §102(b) as being anticipated by Capecchi be withdrawn.

All issues raised by the Office Action dated August 28, 2002, have been addressed in this Reply. Accordingly, a Notice of Allowance is next in order. If the Examiner has any further questions or issues to raise regarding the subject application, it is respectfully requested that she contact the undersigned so that such issues may be addressed expeditiously.

Respectfully submitted,
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